MINAR International Journal of Applied Sciences and Technology
ISSN: 2717-8234
Article type: Review Article

Received: 18/10/2022 **Accepted:** 01/11/2022 **Published:** 01/12/2022

BACTERIAL BIOFILM AND HOST IMMUNE SYSTEM

Fatima Rammadan ABDUL [1]

Mustansiriyah University, Iraq

Mohammed Twfeek Abdul HUSSEIN [2]

Mustansiriyah University, Iraq

Alaa L. ABDULLAH

Rusafa Third, Iraq

Abstract:

Biofilms measure prevalent in environment and represent a very essential approach enforced by germs to persist in generally severe environments. They will be useful or have a opposing impact significantly once shaped in trade surroundings or on medicinal devices. By way of, analysis into the development and removal of slime layer is vital for several castigations. Several new practices are recently advanced for, or tailored to, biofilm studies that have subsidized to deeper data on biofilm physiology, arrangement and arrangement. during this assessment make a case for the characteristic biofilm additionally the} stage of the formation also make a case for but cell to cell communication .Show example of gram positive and negative microorganism formation biofilm conjointly however biofilm antibiotic tolerance. Antibiotic resistance may be a pertinent topic today, demonstrating one in each of the foremost reasons of infection-connected death and illness at a world level. This development is worrying and represents a neighborhood of importance for every medical follow and basic analysis. One vital mechanism whereby being gain resistance to antibacteria and avoid the method is by creating slime layer. it's projected that ~80% of the being creating chronic infections can kind biofilms. throughout the tactic of biofilm formation bacteria have the flexibleness to talk by every additional done assemblage detecting.

Keywords: Immune System, Biofilm, S.Aureus, Natural Immunity, Acquired Immune.

http://dx.doi.org/10.47832/2717-8234.13.6

[1] qetasyshah@gmail.com, https://orcid.org/0000-0001-7590-4221

[2] mht1695@uomustansiriyah.edu.iq

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Introduction:

Biofilm every society of microbes within cells employees to every different and sometimes conjointly to a flatness. These adherent cells become entrench among a sticky animate thing matrix that's composed of animate thing chemical compound substances (EPS) [1]. The cells inside the biofilm turn out the EPS parts, that area unit generally a chemical compound hodgepodge of animate thing, lipids ,proteins, polysaccharides and desoxyribonucleic acid [2].For the reason, that they need three-dimensional framework & seem a communal life style for bacteria, they need metaphorically delineate as "cities for microbes [3;4]. Biofilms might type arranged lifeless or alive surfaces &might be predominant in hospital settings, natural, and industrial [5]. The microbes cells developing in an especially biofilm area unit physiologically not like since organisms of an correspondent organism, which, via in equality, area unit single-cells that will swim or float in an exceedingly liquefied medium [6]. Bacteria type a biofilm in reaction to numerous different factors,[7] which can embody cellular appreciation of specific or non-specific connection locates on organic process cues ,surface or in specific suitcases by introduction cells of organism to concentrations of sub-inhibitory of antibiotics.[8,9] A cell that changes to the biofilm form of development suffers a phonotypical transport in conduct within which giant groups of genes area unit differentially controlled [10]. Biofilm formulation maybe a vital virulence mechanism within the pathologic

process of the many medically .

Substantial microorganism pathogens, like *Pseudomonas aeruginosa*[11], staph aureu s [12], and *E. coli* [13]. the amount of infections being associated otherwise attributed with biofilm contagions is major, with some collectiveexamples enclosed inflammation [14]colitis[15], pinkeye [16], periodontal disease [17], urinary tract infection [18], and rubor [19]. Actually, it's foreordained that eighty percentage of whole microbe disease in persons area unit an on the spot results of biofilms [20]. One biofilm-connected infection of special medicinal heed is *P. aeruginosa* slime layer within the lungs of fibrocystic disease of the pancreas patients. This timeserving infectious agent has been illustrious to rise infections respiratory organ diseases that may score in vital mortality and morbidity [21]. Extremely, insistent biofilm-associated wound infections, that usually includes the *S. aureus and P. aeruginosa* [22], area unit prompt to be chargeable for over eightieth of the a hundred limb exclusions administered on diabetic patients in every year [23]. An extra space of significance once as biofilm-connected Infection is deep-seated therapeutic devices.

Biofilm Formation

Biofilm development may be viewed as a growing process consisting of four common characteristics:

A: Attachment

B: Formation of matrix

C: Maturation

D: Dispersal

The mechanisms underlying these attributes area unit immensely completely different from species to species, however they converge to provide terribly similar outcomes (Fig.1).

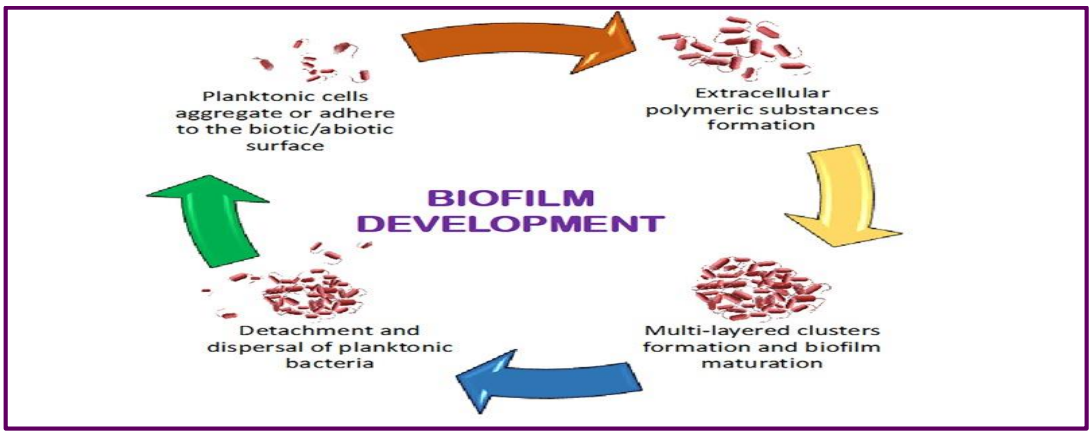

Planktonic cells aggregate or adhere to the biotic/abiotic surface
Extracellular polymeric substances formation
BIOFILM DEVELOPMENT
Detachment and dispersal of planktonic bacteria
Multi-layered clusters formation and biofilm maturation

Figure 1: Biofilm Improvement

A: Attachment

The major step of the biofilm produce method is surface adhesion (Fig.2). Plankton, microorganisms meeting a submerged external and soon develop attached. Reversible adhesion occurs initially and is affected by ecological for example temp, acidity, ionic strength of the medium and addition to microorganism properties like property and motility [24].

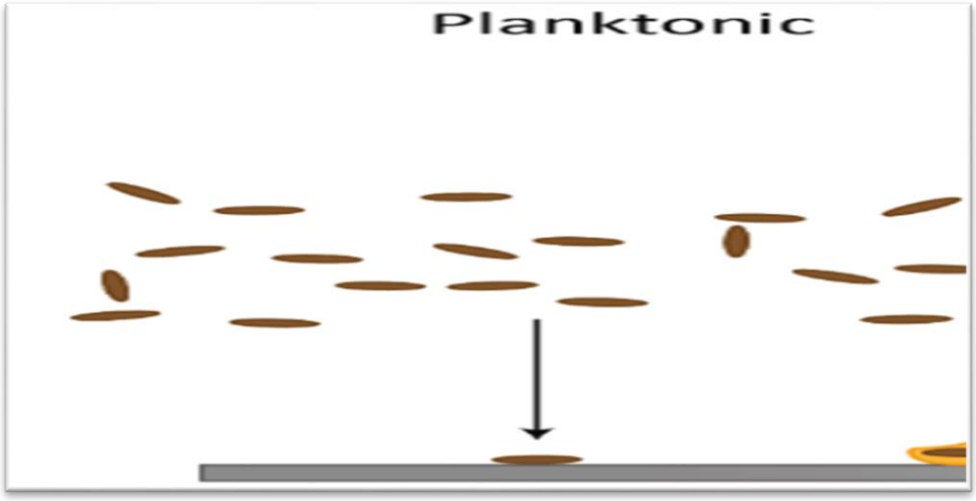


Figure (2): Describe the first stage (Attachment) to foundation biofilm

B: Formation of matrix

Finally the irretrievable bond of bacterium to the surface grosses place , cells begin to supply outer cellular compound substances (EPS) and to colonize the surface. The elements of the matrix will vary wide from biofilm to biofilm counting on the species and also the native atmosphere. for many biofilms [25], the matrix consists:

Table 1: Constituents of the Biofilm Medium

	Components	Percentage of matrix
A	Microbial cells	2-5%
B	DNA and RNA	<1-2%
C	Polysaccharides	1-2%
D	Proteins	<1-2%(including enzyme)
E	Water	Up to 97%

C: Maturation

The third phase in biofilm is development. throughout silme layer maturing, bacterium still increase and manufacture animate thing matrix. By this step, the biofilm assumes a three-dimensional building Fig. (3). This progress is usually thanks to microbial–microbial interactions; many proteins surface and animate thing ground elements area unit concerned in microorganism adhesion and biofilm architecture[24].

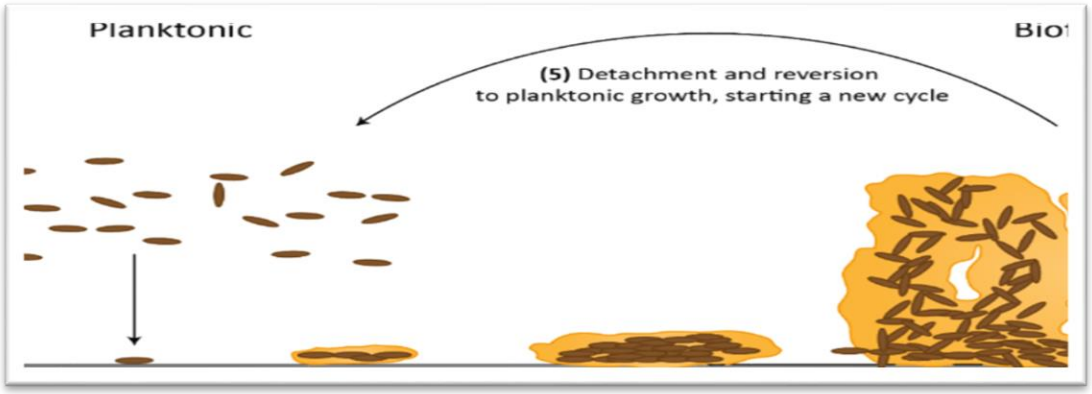
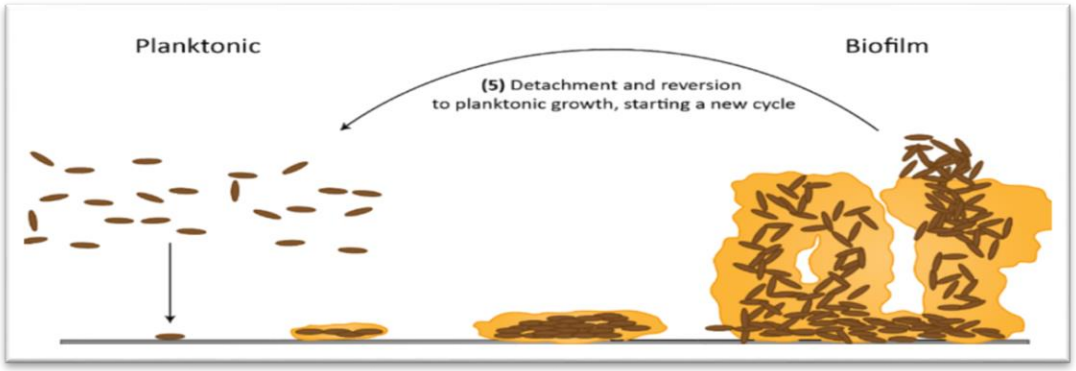


Figure (3): Third Stage (Maturation) when Formation of Biofilm

D: Dissemination

Eventually, if the biofilms reach maturity, they will spread by separating large or small pieces of cells (Figure 4), causing the microorganisms to adhere to a surface or biofilm away from the initial communal [24].



Figuer (4): Illuminate Detachment and Reversion to Planktoic Development and Starting a New Cycle

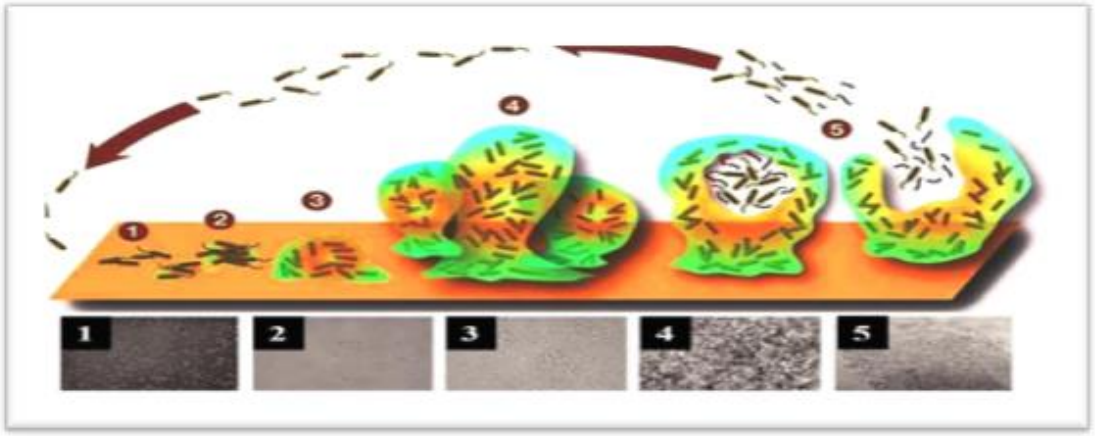


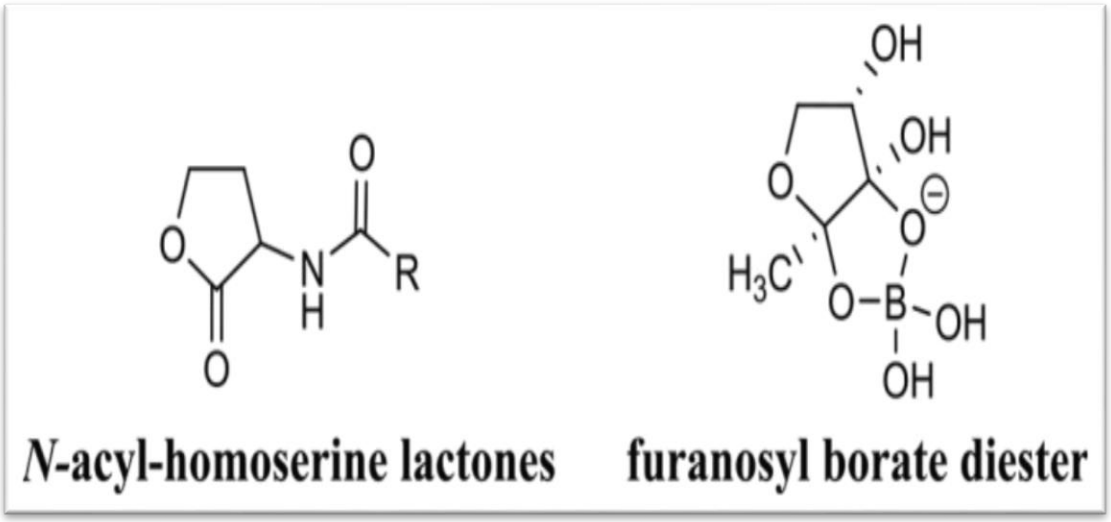
Figure (5): A model showing the standard stage-wise development of a microorganism biofilm in the course of transmitted lightweight research pictures showing these completely different stages for a *P. aeruginosa* biofilm. Republished with permission of Annual Reviews, Inc. [25].

Quorum Sensing

Biofilms square measure noted to observance their residents mass done a cell-to-cell sign method identified as sensing of quorum [25]. Cell-to-cell story may an advanced regulatory operation that prevents biofilm cell wideness from attainment associate indefensible plane [26]. Collecting is depending on signal molecules recognized as auto-activation (Fig. 6). Inducers unit of measurement permanently being produced via the organism, and so, as an example cell density raise, thus can the number of autoinducers (Fig. 7). At a tough and quick cell thickness, a crucial dawn meditation of autoinducers is arrive, that's understood as a result of the gathering level [28]. throughout now, autoinducer receptor attach causes the stimulus of the many aim genes or inhibition. This inflection of the gathering police investigation operation badges microorganism to indicate a combined reaction that edges the whole organism common via partake the optimum biofilm quantity and co-ordination virulence phenotypes [27,28,29].

The identical response is decided to the biofilm by making a sort of cellular organism, permitting the association of the organism population in step with dynamic environmental situations. The adjective sensing element agglomeration isn't thought of a population density.

Sure, aggregation has additionally been revealed to support quickness the repast of advantageous transformation through biofilm organization, improve contact to nutrients, and gift in antibiotic tolerance [29]. Get-together sensing commands the metabolic act of organism, then it canister boost being biofilm development and exaggerated virulence. Throughout this analysis we've a bent to explain the biofilm formation technique, sensing [30], extinction, numerous important infectious microorganism creating biofilm, ways in which of interference & their encounters and limits [31]. The development has been created among the interference and dealing of biofilm - centered sickness, new strategies unit of measurement required and have to be compelled to be any developed[32].



Fiuger (6): Chemical Arrangement of Two Major Kinds of Minor Particle Auto inducers Complex in Quorum Sensing

Homo serine lactone area unit of essential cellular announcement molecules complicated in quorum sensing & cluster homo-serine lactone-reliant is utilized mainly via G-ve bacteria [33]. The AHL particles have in collective the homoserine lactone ring, though, they differ long & alternates. AHLs area unit produced by a particular cognate AHL synthetase. curiously, academic degree hyperbolic concentration of AHL was associated with major being development[34]. AIPs area unit signal molecules concealed by membrane trailers and produced by G+ve [35]. As a result of the ecological attention of AIPs can increase, these AIPs attach to the critical amino alkaloid acid protein device that phosphorylates [36], and as a importance alters target natural phenomenon. In cocci assemblage sensing indicators area unit severely synchronized by the accent sequence regulator or agr that's connected with AIPs exudation. These genes area unit chargeable for the assembly of assorted toxins and degradable external enzymes [37].

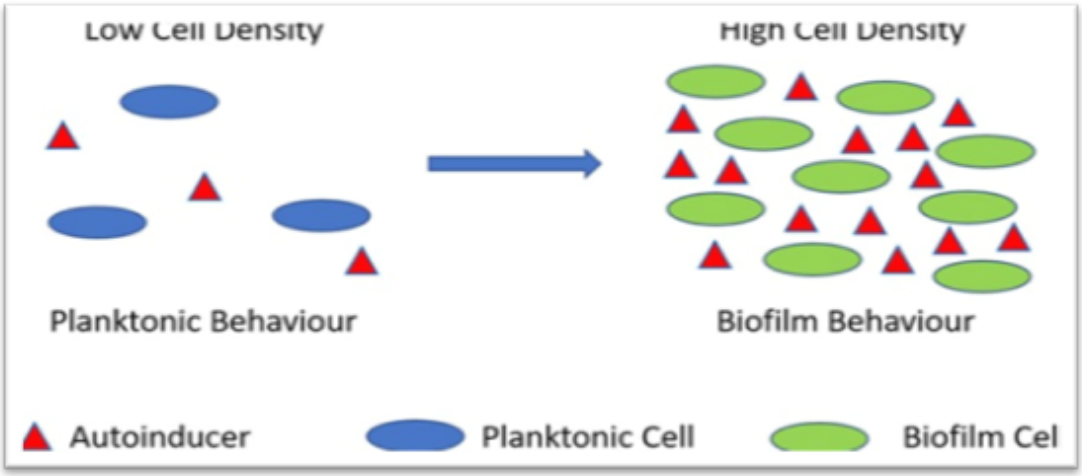


Figure (7) Quorum sensing illustration. throughout organism cell growth (blue ovals), the relative quantity of autoinducers (red triangles) is proportionately low. As cells enter a densely inhabited mode of growth (green ovals) the relative proportion of autoinducers will increase

Via means of a locality of their collaboration & communication, bacteria the flexibleness to intellect &transform the indications after separate strains in AI-2 or auto-inducer-2 interspecies indicators[38], activation via LuxS produce. Furthermore, LuxS worries inside the stimulation of the cycle of methylation, being undisputable to achieve the terms of the many genes connected by the organism procedures of receptor, disinterest, and poison assembly [39].

Alternative Bacterium

Several kinds of germs can end up biofilms& specific will even be anxious in hospital-acquired contagions [41]. Specimens *embrace cocci aureus, genus aeruginosa, escherichia, enteric bacteria , A.baumannii, & Enterococcus spp* [42]. Different samples of biofilm forming microbes ar given in(table 2).

Table 2: Illustrations of bacterial spp. complicated in biofilm development and their natural effects

Bacterial strain	Gram stain	Types of infections
Staphylococcus aureus	Gram-positive	Chronic biofilm infections, right valve endocarditis, chronic wound infection, lung infections in patients with cystic fibrosis
Staphylococcus epidermidis	Gram-positive	Endocarditis, catheter-related infection, joint prosthesis infection
Streptococcus pneumoniae	Gram-positive	Lung infections, bacterial meningitis, acute or chronic otitis media
Listeria monocytogenes	Gram-positive	Co-culture interactions with Pseudomonas, Vibrio strains, listeriosis, contamination of food products
Burkholderia cepacia	Gram-negative	Opportunistic infections in patients with blood cancer
Escherichia coli	Gram-negative	Hemolytic uremic syndrome, acute diarrheic syndrome, urinary tract infections
Klebsiella pneumoniae	Gram-negative	Bacteremia, liver abscess, urinary tract infections
Pseudomonas putida	Gram-negative	Urinary tract infection
Pseudomonas aeruginosa	Gram-negative	Osteomyelitis, ventilator-associated pneumonia, lung infections in patients with cystic fibrosis, opportunistic infections in neutropenic patients, nosocomial infections
Pseudomonas fluorescens	Gram-negative	Bioremediation, biocontrol- Pythium, Fusarium, antimicrobial properties – production of mupirocin

Biofilm tolerant to antimicrobial

Once slime layer-be present in cells are detached since the foremost communal, antibacterial weakness is rapidly reworked for these cells [43]. Therefore, biofilm antibiotic tolerance is expected to include totally different appliances to being anti-germ resistance.

BAT has been made public such as a result of the power of biofilm-exist in germe to continue anti-germ handling via developing their present genes complement [44,45]. BAT square measure usually classified into a pair of groupings: essential (causing from progress throughout a biofilm) & elicited (ensuing as a reaction to antibacterial action). Numerous main innate reasons square measure far-famed that directly effect BAT [46] and shortly mentioned under Fig. (8).

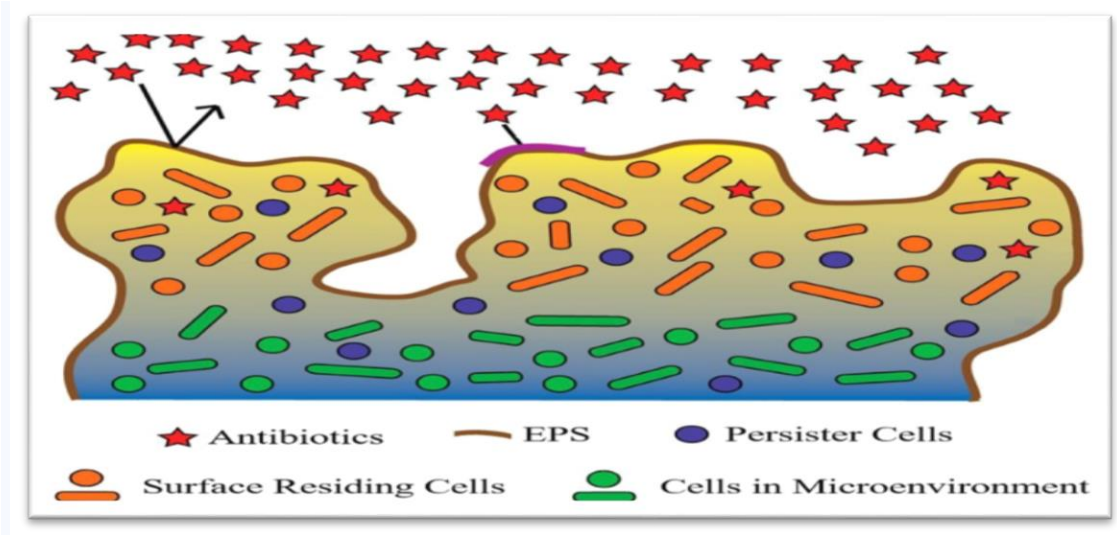


Figure (8) ; Appliances causative to biofilm antibacterial tolerance [68].

Role of biofilms in pathogenesis

Biofilms are establish near anywhere and may influence human health every utterly and harmfully [47]. One instance of a helpful product consist of the biofilms of collective organism like staphylococci epidermidis, which could obstruct the organization of likely pathogenic organism through the encouragement of host-cell immune ramparts & thus interference of bond[48,49]. Though, slime layers square measure extra sometimes related by numerous pathogenic forms of human illnesses and infections of plant [50]. One communal instance is monogenic disease, foremost of conceded hereditary condition in Western Europe. Monogenic disease (CF) patients infected by *P. aeruginosa* [51]. While, contaminating the CF viscus, *P. aeruginosa* experiences a distinguishing change since academic degree severe virulent organism to a CF custom-made organism, permitting it to remain the viscus for years. This is {often this can be} often because of the assembly of the matrix sugar alginate, important to the foundation of a mucous biofilm that tolerates antibiotics [52,53], mechanisms of every the innate and accommodative reaction, and fights activity. The tenacity of these mucoid biofilms within the CF viscus lands up within the event of a particular macromolecule response [54,55]. This stimuli chronic irritation mediate by granulocytes & lands up in simple harm to the viscus tissue of CF patients (see Figure 9 A)[56,57]. A dditional instance for biofilms in human suitability is sign likely principal decay. The ingesting of attainable sugars like sweet drinks or treats reasons rise among assembly & exudation of organic acids via organism create in teeth plaque [58,59]. If absent untreated, the exaggerated process of the biofilm lands up within the demineralization of the coating & thus development of dental caries [60].

Immune System

Chemical barriers, such as those found in the skin and respiratory tracts, help prevent microbial infection. Saliva and tears include antimicrobial peptides and enzymes produced by the skin, including -defensins, lysozyme, and phospholipase A2 additionally, breast milk is antimicrobial. The vaginal secretions associated with the onset of menstruation are considered chemical barriers after they become a little acidic; whereas, semen include zinc, which is fatal to disease factors. In the stomach and digestive tracts, acids and protein enzymes are secreted, which act as a chemical resistance that kills bacteria and many small organisms foreign to the body [61].

The immune system functions in accordance with two immune systems: the innate immunity system, which is inherited from parents and is passed down to children, and acquired immunity (also known as adaptive immunity), which each person develops over the course of their lifetime as a result of diseases to which they are exposed and against which their bodies develop immunity. Although these two immune systems are fundamentally different from one another, they are interrelated and act in concert with one another. These two immune systems each function in accordance with unique mechanisms that activate and boost the effectiveness of the immunological response of the other immune system[62]. More than that, these two immune systems are interconnected since a number of innate immune system chemicals are necessary for acquired immunity to function properly and vice versa. This is the deal, independed on the dependency. The innate immune system helps as the body's original line of protection compared to bacteria pathogenic from the time an antigen is exposed until acquired immunity begins. The body's non-specialized innate immune system can frequently get rid of numerous bacteria, viruses, and external invaders on its own. When innate immunity falters and infections are able to get around it, the acquired immune system improves the immune system's effectiveness[63].

Natural immunity

Gene-encoded, non-clonal humoral and cellular components that make up innate immunity offer general defense against pathogens without being affected by frequent contact with infectious outsiders. Bacteria biofilms were administered to newly isolate human neutrophils and macrophages in order to get the best evidence yet for the presence of an innate immune reaction to bacteria in biofilms [64]. The biofilm bacteria were killed through phagocytosis, accumulation, penetration, and respiratory burst, according to the observed reactions. Human neutrophils and monocytes have also been shown to have antimicrobial action against the *in vitro* biofilms of, S. mutans, S. aureus& C. albicans [65].

The buildup of active The innate immune response to lung infections caused by *P. aeruginosa* biofilms includes neutrophils in the airways, according to sampling done before the formation of the active immune response during lung infections caused by biofilms in mice [66]. The interactions of *P. aeruginosa* slime layer, neutrophils& macrophages through the continuing lung infection in cystic fibrosis patients were the focus of these studies (CF). Because of the association among lung tissue injury &the endobronchial increase of active neutrophils [67], by action evidenced via a persistent breathing burst &the production of nitric oxide, the response via neutrophils has attracted specific interest in this circumstance. Additionally, neutrophil activity-related proteases and oxidative lesions are linked to lung tissue damage [68].

By activating neutrophils through TLR9-independent methods, bacterial eDNA, a matrix component of biofilms, can increase intracellular signaling and IL-8 production. By the fucoid phenotype being known by way of the main virulence factor in patients with CF, who have a chronic infection, alginate is another widely present component of the matrix in the mucoid *P. aeruginosa* biofilm [69].

Alginate may cause neutrophils to have an enhanced respiratory burst, and it may also cause monocytes to generate cytokines in a lab setting. Monocyte activation by polymeric alginate components generated by *P. aeruginosa* is thought to be mediated via TLR2 and TLR4 [70], while the activation of neutrophil receptors is still a mystery. Alginate is not the only polysaccharide present in the matrix of *P. aeruginosa* biofilms; Psl and Pel may also be able to elicit a biofilm-specific innate immune response. Given that the presence of biofilm-specific proteomes has been contested [71], an innate immune response unique to biofilm is less likely to be triggered against proteins.

• Phagocytes, including macrophages and neutrophil granulocytes, are cells with the specific function of ingesting, destroying, and digesting different bacteria. Natural killer cells, which include lymphocytes and granuloma cells, are crucial for warding off infections and cancerous cells.

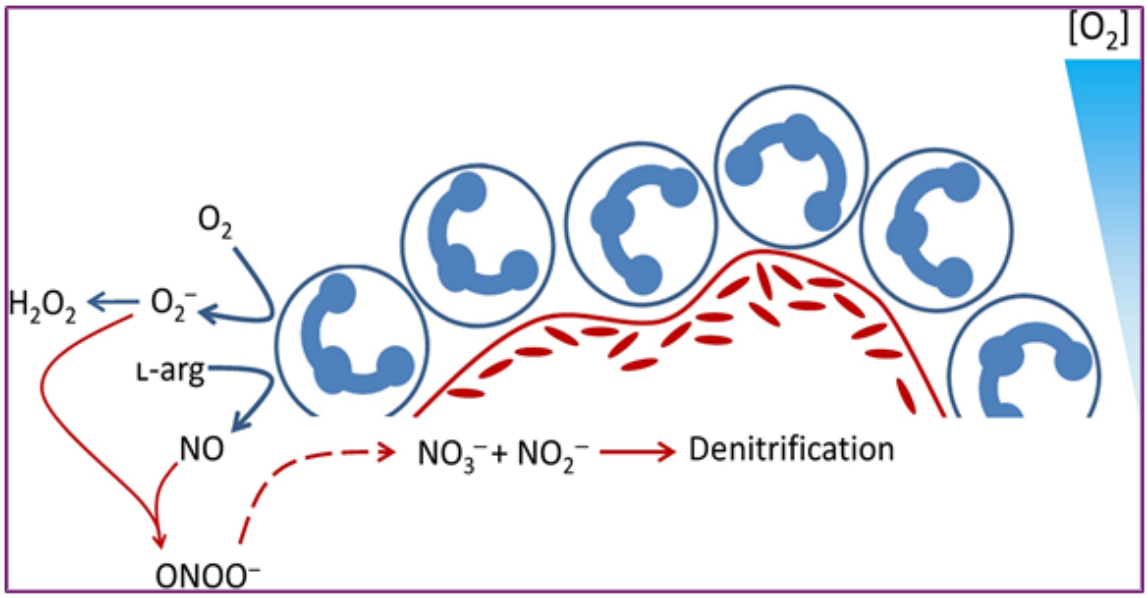


Figure-9:A schematic example of host–biofilm interaction: In CF lungs, mucus-embedded neutrophils (blue) deplete O_2 in the production of ROS including superoxide (O_2-) and hydrogen peroxide (H_2O_2). O_2- reacts with reactive nitrogen species (RNS) to form peroxynitrite, decomposing to nitrate (NO_3-) and nitrite (NO_2-). These N-oxides feed into the denitrification pathway in anoxic *Pseudomonas aeruginosa* biofilms (red) to generate energy for anaerobic growth.

• Acquired Immunity and biofilm

After being exposed to germs and viruses that cause disease, an organism develops acquired immunity. The way in which its substances function is distinctive since each of their cells or particles can only respond against one specific pathogen antigen. The acquired immune response varies from person to person depending on the acquired immune factors that each person's body went through individually and depending on the pathogens that he was exposed to during his life, in contrast to the natural immunity, which is similar in individuals of a particular species. The capacity to develop an immunological memory is an additional characteristic of acquired immunity. T and B cell lymphocytes are portion of the acquired immunity. Early vertebrates developed the adaptive immune response, which enhanced immune response and triggered immunological memory, in which each pathogen is "remembered" by an antibody signature. [68] The antigen presentation method used by the adaptive immune response to identify a particular invader (antigen) is known as antigen presentation. Due to the antigen's specificity, the immune system is able to produce reactions that are intended to neutralize it or disease-carrying cells. Memory cells in the body keep the ability to recall actions. Specialized memory cells recall a sick antigen if it enters the body more than once and attempt to quickly get rid of it.

Note: Several terminologies are used in this article because there are many author.

Specialized leukocytes and T cells make up the adaptive immune system's cells. Major lymphocyte types that develop B cells and T cells are produced by hematopoietic stem cells in the bone marrow. T cells participate in cell-mediated immunity, whereas B cells take part in the humeral immunological response. Together B &T cells have receptor molecules that can identify exact germs or viruses as antigens. Only once the antigen releases tiny fragments of itself that are presented with a "self" receptor molecule known as the major histocompatibility complex (MHC)[70] do T cells detect a so-called "non-self target," such as an antigen.

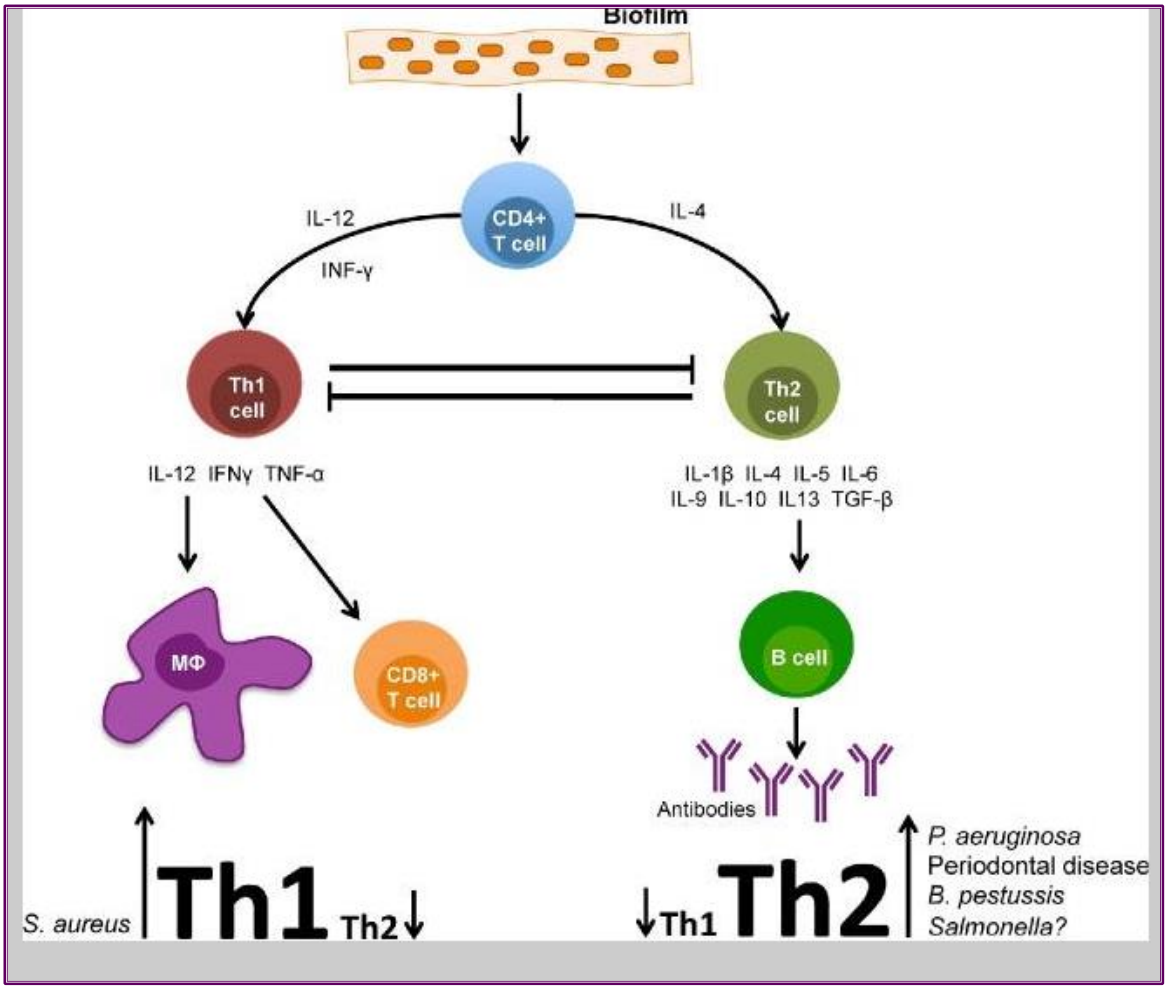


Figure 10: Diagram of the immune response to a bacterial biofilm.

According to Medzhitov and Janeway (2000), CD4+ helper T cells activate cytotoxic T , B cells & macrophages upon activation, demonstrating a regulatory role in AI (Fig.10). Type 1 Th produce interferon-gamma (IFN-), IL-2, and TNF-; type 2 Th produce TNF- and IL-6[71]. These signals trigger cell-mediated immunity, opsonization, complement-fixing antibodies from B cells, macrophage activation, and phagocyte-dependent inflammation . As an alternative, type 2 Th controls the production of immunoglobulins and produces Interleukin -4, IL-5, IL-6, IL-9, IL-10, and IL-13. Type 2 Th also promote eosinophil differentiation and are antagonistic to phagocytes. In the end, these effects reduce the pro-inflammatory environment. A fresh subpopulation of Th cells was identified about ten years ago. IL-17A, IL-17F, IL-21, and IL-22 are produced by Th17 cells[72].

The acquired immune system is activated through the mediating effects of macrophages (M) &dendritic cells (DC), both of which are essential for optimal activation. These cells are specialized in antigen uptake as immature DCs, specifically in antigen-exposed sites like

mucosal surfaces and secondary lymphoid tissue [73]. These cells develop into mature DCs with specialized antigen processing and presentation with antigen absorption and cytokine exposure, primarily from the inflammatory response. Therefore, the DCs act as starting cells for the acquired immune response when a pathogen (or antigen) is initially encountered. An important link between the innate immune system and the adaptive immune system, DCs are expert antigen-presenting cells [74].

Since DCs are extremely malleable cells, their environment and level of activation both influence their surface phenotype. Since there are few DCs in the tissue, isolating them can be challenging and time-consuming, especially in investigations involving humans. A mouse typical of chronic *P. aeruginosa* lung disease has demonstrated pulmonary DC engagement[75].

CONCLUSIONS:

Most organisms have the ability to produce biofilms. From a medical point of view, the biofilm is a serious problem, as it not only causes severe infections, but also has a high ability to resist most antibiotics, which explains the tolerance of these microbes to the human immune system and antimicrobials. In addition, our knowledge of the stages and formation of the biofilm in many microbes Antimicrobial resistance can be controlled by knowing how to dismantle and analyze these membranes, which are a barrier to antimicrobial resistance and bacterial resistance to most of the body's immune systems.

Reference:

1- López, Daniel; Vlamakis, Hera; Kolter, Roberto (2010). "Biofilms". Cold Spring Harbor Perspectives in Biology. 2 (7): a000398. doi:10.1101/cshperspect.a000398. ISSN 1943-0264. PMC 2890205. PMID 20519345.

2- Aggarwal, S; Stewart, P; Hozalski, R (2016). "Biofilm Cohesive Strength as a Basis for Biofilm Recalcitrance: Are Bacterial Biofilms Overdesigned?". Microbiology Insights. 8 (Suppl 2): 29–32. doi:10.4137/MBI.S31444. PMC 4718087. PMID 26819559.

3- Yankholmes, A. (2018). Tourism as an exercise in three-dimensional power: Evidence from Ghana. *Tourism management perspectives*, *25*, 1-12.

4- Watnick, P.; Kolter, R. (2000). "Biofilm, city of microbes". Journal of Bacteriology. 182 (10): 2675–2679.

5- Lear G, Lewis GD, eds. (2012). Microbial Biofilms: Current Research and Applications. Caister Academic Press. ISBN 978-1-904455-96-7.

6- O'Toole, G. A.; Kolter, R. (1998). "Initiation of biofilm formation in Pseudomonas fluorescens WCS365 proceeds via multiple, convergent signalling pathways: a genetic analysis". Molecular Microbiology. 28 (3): 449–461. doi:10.1046/j.1365-2958.1998.00797.x. ISSN 0950-382X. PMID 9632250.

7- O'Toole, G. A.; Kolter, R. (1998). "Flagellar and twitching motility are necessary for Pseudomonas aeruginosa biofilm development". Molecular Microbiology. 30 (2): 295–304.

8- Karatan E, Watnick P (2009). "Signals, regulatory networks, and materials that build and break bacterial biofilms". Microbiology and Molecular Biology Reviews. 73 (2): 310–47.

9- Hoffman LR, D'Argenio DA, MacCoss MJ, Zhang Z, Jones RA, Miller SI. (2005). "Aminoglycoside antibiotics induce bacterial biofilm formation". Nature. 436 (7054): 1171–5.

10- An D, Parsek MR. (2007). "The promise and peril of transcriptional profiling in biofilm communities". Current Opinion in Microbiology. 10 (3): 292–6.

11- Gellatly S. L., Hancock R. E. (2013). Pseudomonas aeruginosa: new insights into pathogenesis and host defenses. Pathog. Dis. 67, 159–173. 10.1111/2049-632X.12033

12- Gordon R. J., Lowy F. D. (2008). Pathogenesis of methicillin-resistant Staphylococcus aureus infection. Clin. Infect. Dis. 46, S350–S359. 10.1086/533591.

13- Beloin C., Roux A., Ghigo J. M. (2008). Escherichia coli biofilms. Curr. Top. Microbiol. 322, 249–289. 10.1007/978-3-540-75418-3_ 12.

14- Machado D., Castro J., Palmeira-de-Oliveira A., Martinez-de-Oliveira J., Cerca N. (2016). Bacterial vaginosis biofilms: challenges to current therapies and emerging solutions. Front. Microbiol. 6:1528. 10.3389/fmicb.2015.01528.

15-von Rosenvinge E. C., O'May G. A., Macfarlane S., Macfarlane G. T., Shirtliff M. E. (2013). Microbial biofilms and gastrointestinal diseases. Pathog. Dis. 67, 25–38. 10.1111/2049-632X.12020.

16- Behlau I., Gilmore M. S. (2008). Microbial biofilms in ophthalmology and infectious disease. Arch. Ophthalmol. 126, 1572–1581. 10.1001/archopht.126.11.1572.

17- Vieira Colombo A. P., Magalhães C. B., Hartenbach F. A., Martins do Souto R., Maciel da Silva-Boghossian C. (2016). Periodontal-disease-associated biofilm: a reservoir for pathogens of medical importance. Microbial. Pathog. 94, 27–34. 10.1016/j.micpath.2015.09.009.

18- Delcaru C., Alexandru I., Podgoreanu P., Grosu M., Stavropoulos E., Chifiriuc M. C., et al. . (2016). Microbial biofilms in urinary tract infections and prostatitis: etiology, pathogenicity, and combating strategies. Pathogens 5:65. 10.3390/pathogens5040065.

19- Post J. C. (2001). Direct evidence of bacterial biofilms in otitis media. Laryngoscope 111, 2083–2094. 10.1097/00005537-200112000-00001.

20- Davies D. (2003). Understanding biofilm resistance to antibacterial agents. Nat. Rev. Drug Discov. 2, 114–122. 10.1038/nrd1008.

21- Wagner V. E., Iglewski B. H. (2008). P. aeruginosa biofilms in CF infection. Clin. Rev. Allergy Immunol. 35, 124–134. 10.1007/s12016-008-8079-9.

22- Omar A., Wright J. B., Schultz G., Burrell R., Nadworny P. (2017). Microbial biofilms and chronic wounds. Microorganisms 5:9. 10.3390/ microorganisms5010009.

23- James G. A., Swogger E., Wolcott R., Pulcini E. D., Secor P., Sestrich J., et al. . (2008). Biofilms in chronic wounds. Wound Repair Regen. 16, 37–44. 10.1111/j.1524-475X.2007.00321.x.

24- Lee CK, et al.(2018). Multigenerational memory and adaptive adhesion in early bacterial biofilm communities. Proc Natl Acad Sci USA. 2018;115:4471–4476.

25- Hiltunen A.K. , Savijoki K., Nyman T.A., Miettinen I., Ihalainen P., Peltonen J., Fallarero A.(2019). Structural and Functional Dynamics of Staphylococcus aureus Biofilms and Biofilm Matrix Proteins on Different Clinical Materials. Microorganisms. pii: E584. doi: 10.3390/microorganisms7120584.

26- Stoodley P., Sauer K., Davies D. G., Costerton J. W. (2002). Biofilms as complex differentiated communities. Annu. Rev. Microbiol. 56, 187–209. 10.1146/annurev.micro.56.012302.160705.

27- Nadell C. D., Xavier J. B., Levin S. A., Foster K. R. (2008). The evolution of quorum sensing in bacterial biofilms. PLoS Biol. 6:e14. 10.1371/journal.pbio.0060014.

28- Annous B. A., Fratamico P. M., Smith J. L. (2009). Quorum sensing in biofilms: why bacteria behave the way they do. J. Food Sci. 74, R24–R37. 10.1111/j.1750-3841.2008.01022.

29- Dickschat J. S. (2010). Quorum sensing and bacterial biofilms. Nat. Prod. Rep. 27, 343–369. 10.1039/b804469b.

30-Preda, V. G., & Săndulescu, O. (2019). Communication is the key: biofilms, quorum sensing, formation and prevention. *Discoveries*, *7*(3).

30- Hannan S., Ready D., Jasni A. S., Rogers M., Pratten J., Roberts A. P. (2010). Transfer of antibiotic resistance by transformation with eDNA within oral biofilms. FEMS Immunol. Med. Microbiol. 59, 345–349. 10.1111/j.1574-695X.2010.00661.x .

31- Sikdar, R., & Elias, M. (2020). Quorum quenching enzymes and their effects on virulence, biofilm, and microbiomes: a review of recent advances. *Expert review of anti-infective therapy*, *18*(12), 1221-1233.

32- Sikdar, R., & Elias, M. (2020). Quorum quenching enzymes and their effects on virulence, biofilm, and microbiomes: a review of recent advances. *Expert review of anti-infective therapy*, *18*(12), 1221-1233.

33- Liu, X., Wang, W., Li, J., Li, Y., Zhang, J., & Tan, H. (2021). A widespread response of Gram-negative bacterial acyl-homoserine lactone receptors to Gram-positive Streptomyces γ-butyrolactone signaling molecules. *Science China Life Sciences*, *64*(10), 1575-1589.

34-Hartmann, A., Klink, S., & Rothballer, M. (2021). Importance of N-Acyl-Homoserine Lactone-Based Quorum Sensing and Quorum Quenching in Pathogen Control and Plant Growth Promotion. *Pathogens*, *10*(12), 1561.

35- Wang, M., Zhu, P., Jiang, J., Zhu, H., Tan, S., & Li, R. (2020). Signaling molecules of quorum sensing in bacteria. *Reviews in Biotechnology and Biochemistry*.

36- Wang, B., Zhao, A., Xie, Q., Olinares, P. D., Chait, B. T., Novick, R. P., & Muir, T. W. (2017). Functional plasticity of the AgrC receptor histidine kinase required for staphylococcal virulence. *Cell chemical biology*, *24*(1), 76-86.

37-Nag, M., Lahiri, D., Ghosh, A., Das, D., & Ray, R. R. (2021). Quorum sensing. In *Biofilm-mediated diseases: Causes and controls* (pp. 21-45). Springer, Singapore.

38- Stephens, K., & Bentley, W. E. (2020). Synthetic biology for manipulating quorum sensing in microbial consortia. *Trends in microbiology*, *28*(8), 633-643.

39- Fleitas Martínez, O., Rigueiras, P. O., Pires, A. D. S., Porto, W. F., Silva, O. N., de la Fuente-Nunez, C., & Franco, O. L. (2019). Interference with quorum-sensing signal biosynthesis as a promising therapeutic strategy against multidrug-resistant pathogens. *Frontiers in cellular and infection microbiology*, *8*, 444.

40- Costerton J, Montanaro L, Arciola C.(2005). Biofilm in implant infections: its production and regulation. The International Journal of Artificial Organs. 28(11):1062–8.

41- Monegro, A. F., Muppidi, V., & Regunath, H. (2020). Hospital acquired infections. *Statpearls [Internet]*.

42- Vila, J. O. R. D. I., Moreno-Morales, J., & Ballesté-Delpierre, C. (2020). Current landscape in the discovery of novel antibacterial agents. *Clinical Microbiology and Infection*, *26*(5), 596-603.

43- Lahiri, D., Nag, M., Ghosh, A., Das, D., Dey, A., Mukherjee, D., ... & Ray, R. R. (2021). Biofilm and antimicrobial resistance. In *Biofilm-Mediated Diseases: Causes and Controls* (pp. 183-208). Springer, Singapore.

44- Yu, Z., Tang, J., Khare, T., & Kumar, V. (2020). The alarming antimicrobial resistance in ESKAPEE pathogens: Can essential oils come to the rescue?. *Fitoterapia*, *140*, 104433.

45- K Satputea, S., G Banpurkar, A., M Banat, I., N Sangshetti, J., H Patil, R., & N Gade, W. (2016). Multiple roles of biosurfactants in biofilms. *Current pharmaceutical design*, *22*(11), 1429-1448.

46- Yonghua, Q., Zhao, W., Wang, T., Fangying, P., Yue, M., Li, F., ... & Li, H. (2020). Proteomic analysis of the antimicrobial effects of sublethal concentrations of thymol on Salmonella enterica serovar Typhimurium. *Applied microbiology and biotechnology*, *104*(8), 3493-3505.

47-Skalny, A. V., Rink, L., Ajsuvakova, O. P., Aschner, M., Gritsenko, V. A., Alekseenko, S. I., ... & Tinkov, A. A. (2020). Zinc and respiratory tract infections: Perspectives for COVID-19. *International journal of molecular medicine*, *46*(1), 17-26.

48- Dufour, D., Leung, V., & Lévesque, C. M. (2010). Bacterial biofilm: structure, function, and antimicrobial resistance. *Endodontic Topics*, *22*(1), 2-16.

49-Szulc-Dąbrowska, L., Bossowska-Nowicka, M., Struzik, J., & Toka, F. N. (2020). Cathepsins in Bacteria-Macrophage Interaction: Defenders or Victims of Circumstance?. *Frontiers in cellular and infection microbiology*, *10*.

50-Drolia, R., & Bhunia, A. K. (2019). Crossing the intestinal barrier via Listeria adhesion protein and internalin A. *Trends in microbiology*, *27*(5), 408-425.

51- Motaung, T. E., Peremore, C., Wingfield, B., & Steenkamp, E. (2020). Plant-associated fungal biofilms—knowns and unknowns. *FEMS Microbiology Ecology*, *96*(12), fiaa224.

52- Rossi, E., La Rosa, R., Bartell, J. A., Marvig, R. L., Haagensen, J. A., Sommer, L. M., ... & Johansen, H. K. (2021). Pseudomonas aeruginosa adaptation and evolution in patients with cystic fibrosis. *Nature Reviews Microbiology*, *19*(5), 331-342.

53- Jurado-Martín, I., Sainz-Mejías, M., & McClean, S. (2021). Pseudomonas aeruginosa: An Audacious Pathogen with an Adaptable Arsenal of Virulence Factors. *International Journal of Molecular Sciences*, *22*(6), 3128.

54- Singh, A. K., Gaur, V., & Maurya, A. K. (2019). The Role of Biofilm in Originating, Mediating, and Proliferating Infectious Diseases. In *Biofilms in Human Diseases: Treatment and Control* (pp. 43-57). Springer, Cham.

55-Maurice, N. M., Bedi, B., & Sadikot, R. T. (2018). Pseudomonas aeruginosa biofilms: host response and clinical implications in lung infections. *American journal of respiratory cell and molecular biology*, *58*(4), 428-439.

56-Maurice, N. M., Bedi, B., & Sadikot, R. T. (2018). Pseudomonas aeruginosa biofilms: host response and clinical implications in lung infections. *American journal of respiratory cell and molecular biology*, *58*(4), 428-439.

57- Aulakh, G. K. (2018). Neutrophils in the lung:"the first responders". *Cell and tissue research*, *371*(3), 577-588.

58- Sodhi, C. P., Wohlford-Lenane, C., Yamaguchi, Y., Prindle, T., Fulton, W. B., Wang, S., ... & Jia, H. (2018). Attenuation of pulmonary ACE2 activity impairs inactivation of des-Arg9 bradykinin/BKB1R axis and facilitates LPS-induced neutrophil infiltration. *American Journal of Physiology-Lung Cellular and Molecular Physiology*, *314*(1), L17-L31.

59-Nyvad, B., & Takahashi, N. (2020). Integrated hypothesis of dental caries and periodontal diseases. *Journal of oral microbiology*, *12*(1), 1710953.

60-Yacoub, A., & Karmally, W. (2017). Nutrition in oral health. In *Nutrition in Lifestyle Medicine* (pp. 193-209). Humana Press, Cham.

61- Metz-Boutigue, M. H., Shooshtarizadeh, P., Prevost, G., Haikel, Y., & Chich, J. F. (2010). Antimicrobial peptides present in mammalian skin and gut are multifunctional defence molecules. *Current pharmaceutical design*, *16*(9), 1024-1039.

62- Wiesner, J., & Vilcinskas, A. (2010). Antimicrobial peptides: the ancient arm of the human immune system. *Virulence*, *1*(5), 440-464.

63- Rauw, W. M. (2012). Immune response from a resource allocation perspective. *Frontiers in genetics*, *3*, 267.

64- Rosenberg, E., & Zilber-Rosenberg, I. (2016). Microbes drive evolution of animals and plants: the hologenome concept. MBio, 7(2), e01395-15.

65- Gombart, A. F., Pierre, A., & Maggini, S. (2020). A review of micronutrients and the immune system–working in harmony to reduce the risk of infection. *Nutrients*, *12*(1), 236.

66- Abbas, A. K., Lichtman, A. H., & Pillai, S. (2019). *Basic immunology e-book: functions and disorders of the immune system*. Elsevier Health Sciences.

67-Bhunia, A. K. (2018). *Foodborne microbial pathogens: mechanisms and pathogenesis*. Springer.

68- Cooper, E. L. (Ed.). (2018). *Advances in comparative immunology*. Springer.

69- Tort, L., & Balasch, J. C. (2022). Stress and Immunity in Fish. In *Principles of Fish Immunology* (pp. 609-655). Springer, Cham.

70- Rawat, S., Gupta, S., & Mohanty, S. (2019). Mesenchymal stem cells modulate the immune system in developing therapeutic interventions. Immune Response Act. Immunomodul.

71- Lajqi, T. (2019). *Trained sensitization and tolerance development in microglial cells: role of phosphoinositide 3-kinase γ* (Doctoral dissertation, Dissertation, Jena, Friedrich-Schiller-Universität Jena, 2019).

72- Gooderham, M. J., Papp, K. A., & Lynde, C. W. (2018). Shifting the focus–the primary role of IL-23 in psoriasis and other inflammatory disorders. *Journal of the European Academy of Dermatology and Venereology*, *32*(7), 1111-1119.

73-Eisenbarth, S. C. (2019). Dendritic cell subsets in T cell programming: location dictates function. *Nature Reviews Immunology*, *19*(2), 89-103.

74- Fischer, U., & Takizawa, F. (2022). Cellular Immune Responses. In *Principles of Fish Immunology* (pp. 141-176). Springer, Cham.

75- Taefehshokr, S., Parhizkar, A., Hayati, S., Mousapour, M., Mahmoudpour, A., Eleid, L., ... & Taefehshokr, N. (2022). Cancer immunotherapy: Challenges and limitations. *Pathology-Research and Practice*, *229*, 153723.